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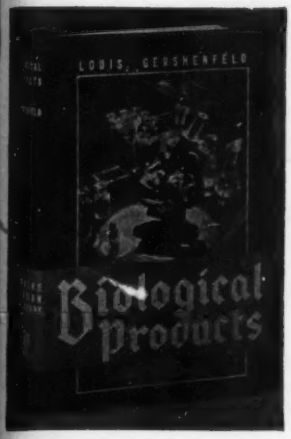

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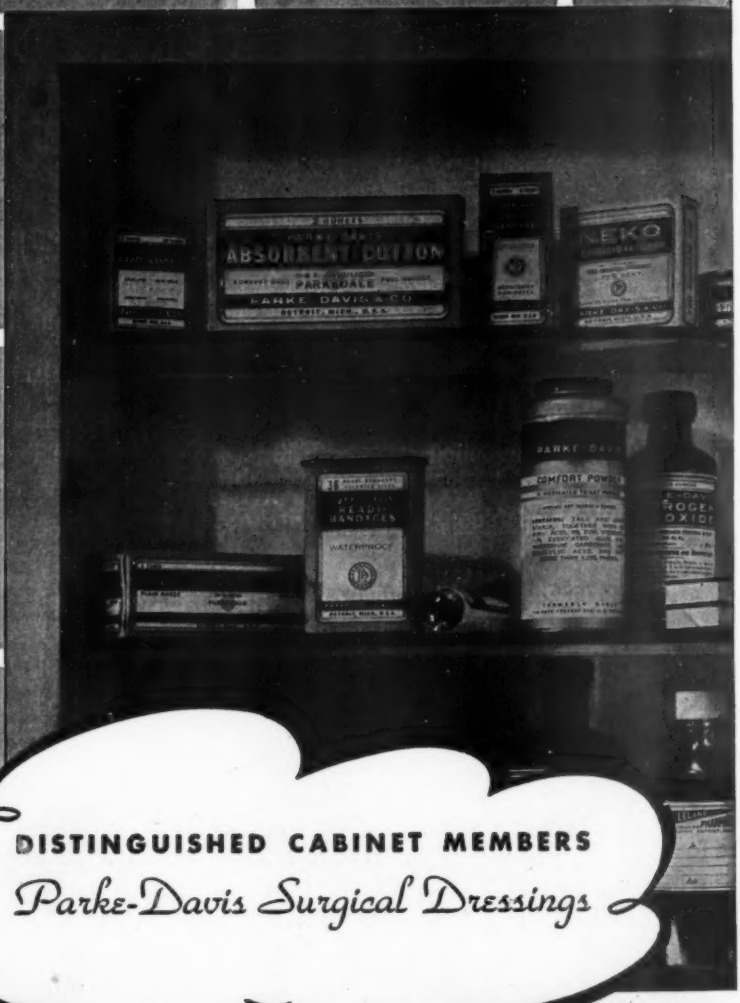

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OUR COVER

DR. IVOR GRIFFITH

IT was with real pleasure that we learned of the recent election of Dr. Ivor Griffith as the forthcoming president of the American Pharmaceutical Association. Those of us who have had the privilege of both study and association with Ivor Griffith know well his qualities of leadership and inspiration.

Like many other outstanding Americans, Dr. Griffith came here from Wales where he was born in 1891, the son of Reverend John and Ann Griffith. And, again, like all Welshmen he possesses that characteristic but indescribable blend of music, poetry and kindness so aptly captured in Llewellyn's classic story "How Green Was My Valley."

When sixteen, young Ivor with his family came to Pennsylvania and was led into the field of pharmacy by Mr. E. K. Eisenhart who encouraged him to attend college. Thus began a career in pharmacy which has ever expanded in both its service ad its influence for the betterment of our profession.

Dr. Griffith is President of the Philadelphia College of Pharmacy and Science, the Association of Science Teachers of the Middle States, and the St. David's Society. For several years he has been an active member of the Pennsylvania State Board of Health. American Pharmacy may well look for constructive accomplishments under his coming administration which cannot but be fraught with diverse and serious problems.

EDITORIAL

FLUORINE AND DENTAL CARIES*

ONE of the foremost public health problems in America is the high incidence of dental caries amongst children and adolescents. It is indeed a pitiful thing to see a child scarcely ten or twelve years of age with first permanent molars, already badly decayed, whereas nature intended them to last a lifetime. There are many factors responsible for this condition, including the cost of dental care which is a social and economic problem. Among the likely etiologic factors we find a number of interrelated possibilities which make the situation quite complex. Thus we have faulty diet, heredity, the chemical character of the saliva, bacterial fermentation, etc.

It has been quite well established that calcium, phosphorus, and vitamins A, D, and C are essential for the development of sound teeth, but an adequate supply of these substances does not *guarantee* absence of caries.

Our grandmothers cautioned us against excessive use of sugar but, with the then newer knowledge of vitamin D, we laughed at such unscientific dogma only to learn now, after careful study, that, whether by intuition or logic, grandmother was indeed right and high sugar diets do increase dental caries. This is believed to be due to the increased activity of the Lactobacillus Acidophilus organisms whose acid attacks and weakens the protective enamel and dentine.

As a result of an interesting chain of investigations a trace of fluorine is now believed to play an important role in decreasing susceptibility to dental caries. About forty years ago a peculiar tooth condition known as mottled enamel was known to exist in certain areas of the west. Investigations of the cause of this condition finally led to the conclusion that it was a condition confined only to certain areas and that the causative effects were exerted only during the period of enamel calcification. Next it was found that the causative

** For those interested in a complete summary of the research in this field, see Borden Review of Nutrition Research, December, 1942.*

agent was carried by the drinking water but all attempts to isolate the substance failed. Not until spectrographic analysis was applied was this riddle solved. By this means it was shown that fluorine in amounts ranging from 2-14 p.p.m. was the etiologic factor involved.

During this long period of study evidence had slowly accumulated that mottled enamel and a low incidence of dental caries were related. This was an even more important observation than the solution of the cause of mottled enamel.

In the last two years some most interesting work has been carried out which proves rather conclusively that traces of fluorine, insufficient to produce mottled enamel, definitely produce resistance to caries if administered to the child during the period of tooth development and calcification.

The amount of fluorine that seems to be indicated is somewhat under 1 p.p.m., an amount which is known not to produce mottled enamel.

The implications of these findings are obvious. It may well be that the inclusion of traces of fluorides in potable water may help rule out the terrific toll on human health and happiness now exacted by dental caries and it merits the attention of those responsible for long range public health planning.

One cannot help but wonder whether in some not far distant day most of man's illnesses and diseases will not be brought under complete control. This, indeed, seems much more of a certainty than does a world completely freed of man's inhumanity to man. In a world of materialism, technologic and scientific advance cannot but exceed social progress.

L. F. Tice.

STERILE MEDICAMENTS*

By Louis Gershenfeld, D. Sc.**

THE use of sterilization is applied in the practical dispensing of medicinal products intended for administration:

(1) Parenterally;

(2) Upon accessible mucous membranes for direct absorption (eyes, nasal passages, tongue, throat, bronchi) or by irrigations, given rectally, through the urethra, by gastric lavage, etc.;

(3) By inunction through the skin or where applied to inflamed surfaces in wounds or by "common ion transfer" (in which penetration of the medicament is aided by the use of the galvanic current);

(4) Infrequently by inhalation; and

(5) At times, medicinal preparations are sterilized merely to preserve them, as they would otherwise decompose rapidly.

Preparations for Parenteral Administration

The value and frequent use of the parenteral administration of medicaments are so well known today as not to require here an extended consideration. It is however best to understand what is meant by the term "parenteral". Some workers employ this as an all-inclusive term to designate the use of any route of administration other than when given orally or rectally. However, the definition as suggested by the author and given on page 219, U. S. P. XII appears more suitable or at least leaves no doubt as to its exact meaning: "The terms 'parenteral' and 'for injection' as used here refer to the administration of a drug under one or more layers of the skin or mucous membranes." It is this therapy which is called by some workers "needle administration", as it is apparent that a needle of some kind is needed in administering the medicament. Parenteral administration is given *intracutaneously* or *intradermally* (between the layers or within the substance of the skin); *subcutaneously* or *hypodermically* (in the lymph spaces under the skin); *intramuscularly* (into the muscular

*Presented at the Midyear Meeting of the American Pharmaceutical Manufacturers' Association, held in New York City, on December 7-8, 1942.

**Professor of Bacteriology, Philadelphia College of Pharmacy and Science.

tissues and lymph spaces); *intravenously* and infrequently *intra-arterially* (into the blood by way of the veins or arteries); into the serous sacs, *intrapleurally, intraperitoneally, intrapericardially,* etc.; into the spinal canal (*intraspinally* or *intrathecal* administration); into the tissues of organs (*intraparenchymally*); and in emergencies into the heart muscle or cavities (*intracardially*).

Regulations for Parenteral Solutions

Not only is a knowledge of the therapeutic use of drugs necessary, but as important, is to have available a detailed knowledge of the source and method of preparation of the product to be administered parenterally. The important requirement of the necessity of having a sterile solution for parenteral administration is obvious, yet about ten years ago when the author directed this to the attention of the profession, some astounding findings were reported in a subsequent survey by the Council on Pharmacy and Chemistry of the A. M. A. (1), resulting from this editorial (2). The need for proper legal supervision over the manufacture and distribution of such preparations became more apparent from these findings. Furthermore, wherever possible, standardization of formulas and uniformity in packaging as far as sizes are concerned are needed in these preparations, even though there is a definite assurance of sterility. Certain methods of sterilization may change or modify the medicaments so treated. The introduction of a variety of different chemicals as stabilizers or as bacteriostatic agents or for other purposes may serve their usefulness in producing a more lasting marketable preparation, but in the final analysis, this may be objectionable, as the added ingredients may yield untoward reactions, or otherwise interfere with the therapeutic efficiency of the preparation upon injection. Such added ingredients may also interfere with the proper performance of suitable assays or identification and other tests for the active medicament. It is obvious that the above should be recognized, and steps taken through some legal avenue to guard against these possible pitfalls. The result has been the regulations as found at present in U. S. P. XII and N. F. VII.

Pyrogens

The use of preparations presumably properly prepared and administered directly into the blood stream (and usually by the intravenous route) results at times in untoward reactions of a nature

different from those reactions displayed by an individual idiosyncracy to a drug or to the presence of known substances which are known or found to be antigenic. In modern therapy and practice, these reactions should be and can be avoided. These reactions appear either only as a slight elevation in temperature (up to 100° F.) which returns to normal quickly, or as a febrile reaction (100° F. or higher) associated with a feeling of cold and pain in the back or legs but no actual rigor, and the most severe kind in which a marked fall in blood pressure and an actual rigor also are present. All of the symptoms are suggestive of protein shock. Inasmuch as the substances causing the latter also produce fever or pyrexial reactions, they are frequently spoken of as "pyrogens". There has been much conjecture concerning the latter, but at present pyrogens are regarded most commonly as dead bacteria (disintegrated or intact), viable but non-pathogenic bacteria, and more frequently as products produced by bacteria (liberated endotoxins or exotoxins). All of these substances are of foreign protein origin. The human body, on the other hand, can tolerate only a limited and a very small amount of foreign protein, when introduced into the circulation. It is apparent that a high incidence of pyrexial reactions from products given by intravenous therapy reflect markedly either on the efficiency of the medicinal preparations used or upon the equipment employed when giving the injection. In either instance, the hazard is avoidable. Intravenous medication is given frequently in serious and desperate conditions. At such occasions especially, when the patient's system is already heavily burdened, any additional effort placed upon the patient, as may occur by untoward reactions of an injection containing pyrogens should be avoided. The use of the greatest care in preparing a safe parenteral product, and scrupulous cleanliness and a careful technique throughout will reduce and even eliminate these reactions.

Water for Injection

The requisites for a satisfactory and safe supply of a pyrogen-free preparation for intravenous use are the employment of scrupulous cleanliness of equipment, apparatus and containers; highest grade chemicals or raw material; pyrogen-free water or pyrogen-free vehicle or solvent; and proper technique of preparation and sterilization. Of these requisites, the use of a pyrogen-free water is probably

the most important factor. In most instances, the other factors are guarded, and care and attention are given to them. On the other hand, the exacting care for freedom from pyrogens in the water used in intravenous preparations is not always given the degree of attention it deserves.

Improperly prepared or "stale" distilled water is most frequently responsible for the production of febrile reactions. In 1911, Wechselmann (3), observed this fact, regarded bacterial contamination responsible, and insisted upon the use of freshly distilled water, after showing that such water does not produce reactions when injected intravenously. Hort and Penfold (4) confirmed these findings. The latter workers and Muller (5) described the bacterial flora of different samples of distilled water, and mentioned those specifically responsible for producing pyrexial reactions. When the first arsenicals were being used, McIntosh and Associates (6) traced the so-called "saline fever" to the distilled water employed. In our own country, Seibert and Associates, who named the fever-producing substance "pyrogen", presented many contributions on fever-producing substances in distilled water (7); temperature variations in the rabbit (8); other protein fevers (9); substances causing febrile reactions following intravenous injection (10); and other works along similar lines (11, 12). It was common to hear the statement years ago that a freshly collected tap water is safer to use for preparing intravenous solutions than a "stale" (old) distilled water. Recently Co Tui and Schrift (13) presented additional data on the production of pyrogens by bacteria.

The above workers demonstrated that bacteria grow in distilled water; old or "stale" distilled water was usually contaminated; freshly distilled water (pyrogen-free), if sterilized immediately, will remain pyrogen-free if kept sterile, but pyrogenic properties are imparted if it is not sterilized, as contamination results from air-borne bacteria; and that the pyrogens were most frequently filterable, soluble bacterial products, removable by distillation, if the latter is properly carried out. Later we find that Banks (14) revealed pyrogens could be rendered innocuous if the solutions containing them are heated to 140° C. for thirty minutes, and Co Tui and Associates (15) found that adsorption filtration was effective in removing pyrogens.

With the wider use of intravenous therapy especially in blood transfusions, a more extensive experience resulted, and as noted by

Lewisohn and Rosenthal (16), reactions were reduced from 12 per cent. to 1.2 per cent. merely by following a scrupulous cleansing technique and using freshly distilled water. The application of these basic principles has definitely proven that reliable intravenous solutions can always be made available. (See: Eggleston *et al.* (17); Titus and Dodds (18); Rademaker (19); Nelson (20); Meade (21); Walter (22), and Whitby (23).)

Preparation of Water for Injection

The technique used to prepare a pyrogen-free water is of greatest importance. We must be assured that the type of apparatus used will provide a pyrogen-free distillate, assuming that all other possible contaminating factors have been eliminated. The still must be fitted with proper baffle arrangements to prevent the carrying over of foreign materials. One of the most frequent causes of contamination is the entrainment by the steam (which becomes the distillate) of droplets of raw water thrown forth as a spray or foam by the ebullition. Careful control of heat and water-flow and especially properly placed well-designed baffles will prevent contamination of the condensers with a spray of raw water, splashed from the surface of the boiling water and thus the subsequent pollution of the distillate. Intelligent operation at all times even of a satisfactory still is essential.

The apparatus and especially the storage vessel for the distilled water must be scrupulously clean and properly protected to prevent contamination. The storage tank should be large enough to hold a working supply for not more than a day. Always drain dry the storage vessel, so as to prevent the growth of bacteria in the residual water, as this contaminated water will pollute subsequent collections of distillate. If the storage vessel is not sterilized, flush with live steam or wash out with several rinsings of pyrogen-free water before using it.

It is apparent that freshly collected pyrogen-free water is not sterile. If allowed to remain without any treatment and especially in a comparatively warm environment, the few bacteria present will grow, and pyrogenic properties will be imparted to the water. To prevent this, pyrogen-free water should be distributed in suitable containers and properly sealed and sterilized in their final containers immediately after distillation. Unused portions of sterile pyrogen-

free water in any container should be discarded or resterilized unless following sterilization, the container is kept closed at all times, and nothing enters but the filtered sterile air needed for replacement. Hermetically-sealed containers of pyrogen-free water or pyrogen-free solutions properly prepared and sterilized can be stored indefinitely with the assurance that the contents kept under these conditions will remain pyrogen-free. Where the pyrogen-free water is to be used for preparing solutions for parenteral use, it is not necessary to sterilize it, but it must be used immediately after distillation for preparing the parenteral solution. This in turn should be prepared, distributed into suitable containers, the latter preferably sealed or protected against the entrance of organisms, and the completed unit preferably sterilized within one working day. If this is not practicable and a bacteriostatic agent is not present, the parenteral solution is compounded with pyrogen-free water as the vehicle, placed in containers holding not more than the amount necessary for a working day, and these working-day batches are stored under refrigeration at a temperature below that at which bacterial growth or deterioration will occur.

Containers for Parenteral Solutions

These containers are usually made of glass. The most satisfactory glassware is that which possesses a high resistance to heat and mechanical shock and also has a stable annealed surface capable of resisting hydrolysis by the contents. For detailed requirements which such containers should meet, see U. S. P. XII, page 567. In washing glassware, insoluble deposits frequently result from the interaction of soaps, detergents and other cleansing agents. This, frequently apparent as a white opalescent film noticeable on dry glassware, is due to the production of insoluble alkali earth soaps. The presence of bacteria, fungi and residues of other organic substances may be encountered. It is therefore apparent that the glassware before being used must be chemically clean. Various cleansing methods are employed preparatory to sterilization. The last rinsing, however, should be with freshly distilled and preferably pyrogen-free water and the containers sterilized, if possible, or dried. If sterilization is not practicable, the cleansing and draining or drying should be performed just prior to the preparation of the parenteral solution.

The containers until used should be placed in suitable positions to protect the inside from dust, then filled, and the contents sterilized at once. Glassware not sterilized or not properly cleansed and finally washed with pyrogen-free water and drained, is apt to contain on the inner surfaces dried pyrogenic substances, and also any moisture remaining may be utilized by the bacteria for further growth.

If the individual containers are not hermetically sealed, care must be observed in the use of the type of stopper which must always be of good quality and sterile. Cotton-stoppered plugs are not to be advocated. In all instances, containers should not be filled to capacity, but sufficient air space should be left above the liquid to prevent the wetting of stoppers during sterilization. The quality and sterility of the contents must not be impaired by improper packaging. The containers should be composed of clear glass, so that the contents can be readily examined. Even if the contents are affected by light, the enclosing of a clear-glass container in a paper tube or a closed carton (impervious to light) to protect the contents is to be preferred to the use of colored or clouded glass containers. It is desirable to market wherever possible only single dose packages. Multiple dose packages should be sold only for those preparations which are to be injected subcutaneously, intradermally and intramuscularly. To avoid the possibility of contamination from the air every time the outside rubber stopper is penetrated, a bacteriostatic agent should be present in the contents of multiple dose vials. Even with these provisions, it is desirable to limit the number of times that penetration of the rubber stopper is made. The only practical procedure is to legalize the volume which can be present in such multiple dose packages, as is now provided by the U. S. P.

Chemicals in Parenteral Solutions

Chemicals only of the highest grade should be used as ingredients in parenteral solutions and especially in the preparation of those for intravenous medication. Particulate matter is present in most containers holding especially bulk chemicals. Dust, dirt, debris and insect parts have been found, though but infrequently in those containers holding high grade materials. Dirty chemicals signify carelessness in handling and present the possibility of contamination with foreign proteins. They should not be used. Transfer of chemicals

should be carried out with the use of suitable implements. The use of hands, dirty implements and scale pans (for weighing) should be avoided. Portions of chemicals which drop on the table and on the balance should be discarded and not returned to the bulk container. Where known quality grades have proven to yield constantly satisfactory finished preparations, it may be desirable to buy only such grades of chemicals of known purity. For instance, it is known that some dextrose samples change during sterilization or storage to a yellow color, mistaken for caramelization. The coloring is due to an aging of levulinic acid. The latter and hydroxymethyl furfural are acid dehydration products, which may form in some dextrose samples during the manufacturing process. In other instances, certain samples of dextrose are found to impart pyrogenic properties to pyrogen-free water. Walter (24) states that "dextrose may contain protein split products, and/or various acid dehydration products of dextrose formed by side reactions during the manufacture of dextrose."

Tests for Pyrogens

It is important to have available a test so as to determine the presence or absence of pyrogenic substances in parenteral solutions and especially in the water used for preparing the latter. Bacteriological examinations are inadequate unless the sample is heavily polluted. Seibert and others have shown that bacterial counts do not necessarily indicate the amount of pyrogen present. It is known that samples of water revealing sterility by the routine techniques may contain pyrogenic substances. Albuminoid ammonia may be present in waters containing the latter, and Knott and Leibel (25) state that an albuminoid ammonia content of 0.005 to 0.025 part per 1000 will always give rise to pyrexial reactions. Albuminoid ammonia, however, is produced by substances other than pyrogens, so that tests for the former are non-specific. Furthermore such tests for albuminoid ammonia are not adapted for routine use. The Ampul Water of N. F. VII must correspond to all tests for Redistilled Water (26). One of the tests for the latter is for oxidizable substances. It is performed by heating 100 cc. of the water to boiling, adding 10 cc. of dilute sulfuric acid, and subsequently 0.1 cc. of twentieth-normal potassium permanganate: the color of the liquid should not completely disappear after boiling for 10 minutes. It is assumed by

some workers that this permanganate test is an indicator of the presence or absence of pyrogens. Since distilled water properly prepared should be free of oxidizable substances and inasmuch as pyrogens are also oxidized readily by boiling permanganate solution, it is assumed that this test may serve as an indicator of the pyrogen content. It is obvious, of course, that this test is not specific for pyrogens, but would be given by most organic substances. Walter (27) suggests frequent examinations to note the purity of water by determining its conductivity: "The distillate from a well-designed properly operated still should have a maximum conductivity of 2×10^{-6} mho at 20° C. One part per million of chloride ion will increase the conductivity of distilled water about 50%." (mho is reciprocal of resistance, ohm.) It is assumed that the presence of electrolytes in freshly distilled water indicates contamination with tap water. This too is a non-specific reaction and like all of the tests described above, it is assumed that the presence of albuminoid ammonia, or substances oxidized by boiling permanganate, or the presence of electrolytes are also polluted with pyrogenic substances. Positive findings are of value. Negative findings are inconclusive. It is, perhaps, somewhat comparable to the sanitary chemical examination as compared to the bacteriological examination of drinking water to detect pollution. The presence of nitrites suggests organic pollution, and the albuminoid ammonia content is regarded as an index of the amount of organic pollution in a sample of water. The absence of nitrite, however, does not mean that the water is necessarily safe; and it is difficult to set an arbitrary standard as to the maximum amount of albuminoid ammonia a good water may contain. The interpretation of certain sanitary analyses is frequently more difficult than the analyses themselves. A chemical sanitary water analysis can only indicate pollution but cannot discover infection. In like manner until a definite and clear-cut relationship can be established between the chemical, physico-chemical and other tests and the absence or presence of pyrogenic substances, no final or conclusive reliance can be placed on negative findings by these tests as indicating the absence of pyrogens.

In the final analysis, however, biological methods must be employed to reveal the actual pyrogen content. Wherever possible, the use of a laboratory test is preferred in which the application is comparable to the conditions as employed in practice, when using the preparation being tested. Injecting the latter into a suitable animal

and noting the production of fever as compared to negative findings with suitable controls supply information much more conclusive than can be given by chemical, physical and bacteriological tests. For the present, the Pyrogen Test given in U. S. P. XII (page 606) appears adequate. Ten cc. of the parenteral solutions are injected into the ear vein of each of 5 healthy rabbits (10 cc. per Kg. of body weight). Rectal temperatures are made hourly for 3 or 4 hours. The rabbit's normal temperature ranges from 38.4° C. (101.2° F.) to 39.4° C. (103° F.). The test is considered positive if three or more of the five animals show an individual rise in temperature of 0.6° C. or more above the normal established for each of the animals injected. Recently Co Tui and Schrift (28) presented a tentative method for testing for pyrogens in distilled water, which involves the use both of the rabbit and dog as test animals. They state that the rabbit is the better animal to test for the absence of pyrogen and the dog is the better animal to establish the presence of pyrogen. The rabbit test dose must not be less than 50 to 100 cc. per Kg., and the test dose in the dog should start from a minimum of 250 cc., since it has been found that the rabbit is three times and the dog is six times less sensitive to pyrogen than man. In performing the test, the solution under examination in amounts of 50 and 100 cc. respectively is injected into two rabbits, not faster than 10 cc. per minute. A temperature rise of 0.5° C. in from one to three hours is taken as presumptive evidence of the presence of pyrogen. Although a positive presumptive test is sufficient to condemn the product as unfit for human use, situations arise in which a confirmatory test is needed. Depending upon the response in rabbits, a dose from 250 cc. to 1000 cc. of the solution under examination is administered intravenously to a dog, not faster than 30 cc. per minute. A rise in temperature of 0.5° C. together with leukopenia, emesis, prostration and diarrhea provide evidence of the presence of pyrogen. At present, a subcommittee of the United States Pharmacopœia is conducting a study of tests for pyrogenic substances. Many of the laboratories of members of this Association are participating in this collaborative study. It is the fond hope of all interested that from this study, there will be made available a reliable, easily performed, and not too costly test.

Sterility Testing

Testing of finished preparations for sterility is the last operation and a most important step in determining the marketability of prod-

ucts for parenteral use. Methods are given in detail both in the N. F. VII and the U. S. P. XII. Different workers have commented on these techniques and various changes have been suggested. It is easy to make changes, but these should be made only after sufficient evidence has been presented that such changes are first, as or still better, more reliable than the existing procedures in detecting bacterial contamination. The fact that there is less time consumed in performing the test or that the procedure is less expensive, or the presentation of similar reasons for making changes should be of secondary consideration. Furthermore, in legalized standard techniques, it is better practice to avoid too frequent changes of such official techniques. When made, they should only be made after a most thorough and comprehensive study has revealed that they can serve a greater usefulness under each and every condition of testing all kinds of preparations and products which must be submitted to such examinations.

It is only within the last decade, that extensive research has been carried out and much experience resulted from the sterility testing of parenteral solutions. Additional information, however, is needed for a more intelligent application of sterility testing techniques. For instance, we know that the pH of a solution or medium influences markedly the growth of different bacteria. Yet in our present methods of testing, the parenteral solution is added to the culture medium and no attempt is made to determine the pH of the final mixture. A uniform technique for testing oily solutions and suspensions should be presented. These are just a few of the problems. Close cooperation between all concerned will result in the introduction of techniques which are all-inclusive, easy to perform and not too costly.

Conclusion

Pharmacy and Medicine have gone far since 1886, when Stanislas Limousin, the French Chemist, devised at the suggestion of Dr. Duhomme, the sealed glass ampul practically as it is employed today. Research has developed tests and procedures to assure uniform and accurate strengths of the contents, the marketing of sterile products, free also from pyrogenic substances and the presentation of safe and potent preparations. Parenteral therapy can only be continued and developed, aided especially by the marketing of appropriate sterile preparations, which are safe and satisfactory in all respects. They must be perfect as is humanly possible to make them. A thorough

knowledge of the many dangers due to unsatisfactory preparations and of the necessary detailed application of the principles necessary, the important ones of which were considered, will make possible the marketing of solutions for use in parenteral therapy which, when injected by any route, will be effective, safe and will not be responsible for avoidable reactions of an objectionable character.

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DELAYED LACTOSE FERMENTATION [1]

By George G. Schaut [2]

EARLY in 1940 the late Dr. John J. Shaw, as Secretary of Health for the State of Pennsylvania, appointed a committee to study and standardize the laboratory procedures, as applied to the testing of water, used by the three major health laboratories supported by public funds, i. e., State Health Laboratory, City of Philadelphia Health Laboratory and the Philadelphia Water Bureau Laboratory. The committee chairman was Colonel Arthur Parker Hitchens, M. C. U. S. A., Director of the Department of Public Health and Preventive Medicine, Medical School, University of Pennsylvania. The writer was a member of this committee. One of the major questions adopted by the committee, at the suggestion of its chairman, was the use of Brilliant Green Lactose Bile (hereafter symbolized by B. G. B.), for the confirmed coliform test.

At one of the meetings Colonel Hitchens referred to some work done in the laboratories of the Connecticut State Department of Health, of which Dr. Friend Lee Mickel is Director (1). This work concerns the late fermentation of lactose by "aberrant coliforms" and their importance in water supplies. This aroused the writer's curiosity as to what might be expected if a longer incubation period should be applied to the tests on the potable water as served to the City of Philadelphia. As our records contained no such previous information it was decided to apply an additional incubation time of 24 hours to all filtered chlorinated water samples collected from the various filter plants and also from samples taken at 30 places in the distribution system. This work was to continue for several years in order to confirm any seasonal variations.

Even an additional 24 hours, making the total incubation period 72 hours does not seem long enough in the opinion of some investigators, for Parr and Friedlander (2) used very long periods of incubation, i. e., 10 days and even 5 to 6 weeks when studying one of the groups as proposed in Stuart's *et al.* (1) classification. Undoubt-

[1] Released for publication through the courtesy of Martin J. McLaughlin, Chief Engineer of Water Bureau.

[2] Chief Chemist, Water Bureau, City of Philadelphia, Pennsylvania.

edly such long periods of incubation uncover organisms that ordinarily would be missed. Such long incubation periods could not be made to fit into any routine examination of a water supply where as many portions are planted as herein recorded.

The total number of inoculative portions (10 cc.), in the case of filtered water basins, for a month hovered around 1000 depending upon the days per month, for samples are collected daily. In the case of the samples from the distribution system, the inoculative portions ran close to 500 per month. Due to pressure of war conditions this work was stopped at the end of June 1942 and thus only a 2-year period is recorded in Fig. 1. As far as climatic conditions are concerned during this 2-year period, it should be recalled that the summer and fall of 1941 showed a great deficiency of rainfall. The term 72-hr. gas refers to those portions that did not produce gas during 48 hours but gas (10 per cent. or over) then appeared by 72 hours, which was or was not confirmed in B. G. B. as the case may be.

Recorded at the same time were those inoculative portions, for both basins and distribution samples, that showed no gas in 24 hours and less than 10 per cent., usually about 5 per cent. or sometimes only a bubble, by 48 hours. These were about equally divided between basin and distribution samples and invariably did not confirm in B. G. B. Of the total inoculative portions their percentage averages 0.10 per cent. Hence, the 10 per cent. datum point for either 24 or 48 hours incubation, established years ago by many pioneers in this field seems to have been well founded.

During the entire 2-year period there were a few inoculative portions that showed no gas in 48 hours and less than 10 per cent. by 72 hours and generally were not confirmed in B. G. B. Here again they were about equally divided between the basin and distribution samples. The average percentage for the 2-year period was approximately 0.10 per cent. for those that did not confirm, and 0.01 per cent. for those that did confirm in B. G. B. The maximum for any one month for those that did not confirm ran 10 fold over the 2-year average, and is also of very little significance. This type of gas formation is, to some investigators way of thinking, really *slow lactose* fermentation and anything else is *delayed* fermentation.

McCrady (3) considers coliform organisms that produce less than 10 per cent. of gas by 48 hours in lactose as slow lactose fermenters and presents the opinion of other workers as well as his own as to their sanitary significance. There is still much discussion

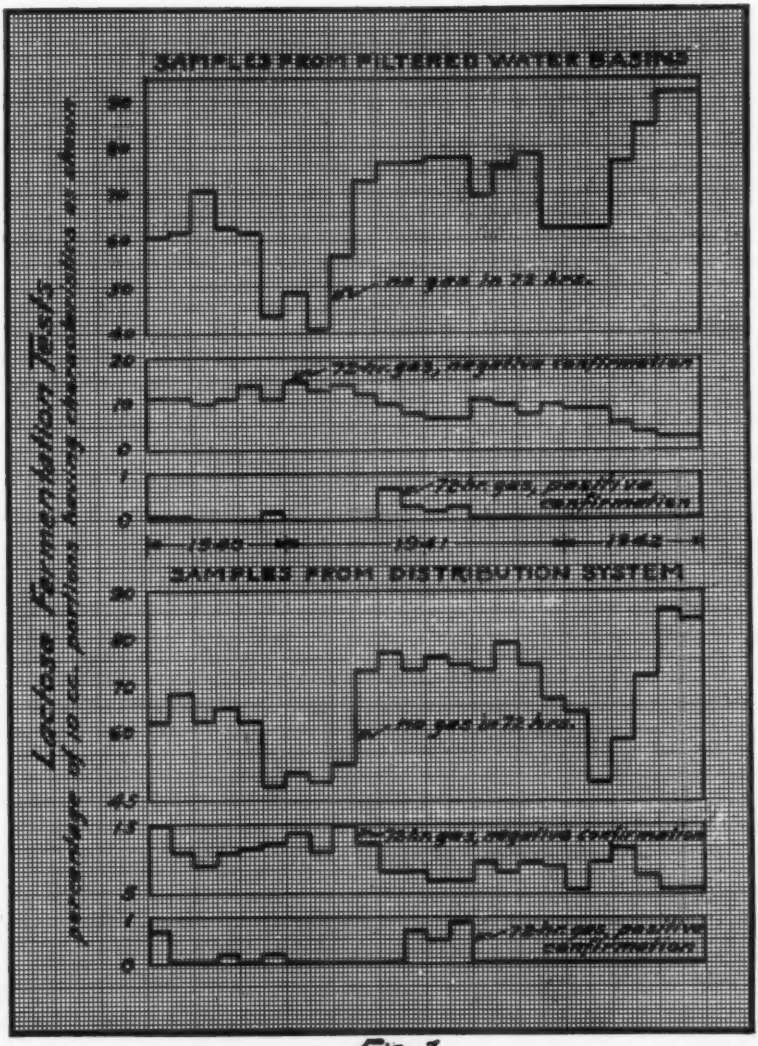

Fig. 1.

as to what the term "slow lactose fermenters" means. Very little light up to the present time has been shed as to the origin of these "slow lactose fermenters". Mallman (4) remarks about delayed fer-

mentation from forms affected but not destroyed by sterilization. Levine (5) found that some waters show a greater number during the summer season. As to the writer's findings with delayed fermentation, those that confirmed in B. G. B. occurred mostly in the summer season (see Fig. 1) although their percentage is so low as to be of no sanitary significance.

Even Hale (6) using B. G. B. for direct inoculation when it was first introduced experimentally (it is still being used for primary inoculation,[3] of course, with certain stipulations and sufficient comparative data to show that on the water which he controls it gives the same coli index much sooner than when it is used as a confirmatory medium) speaks of devitalized B. Coli from stored, filtered or chlorinated waters. "*B. coli* from the disturbed sediment of aqueducts or pipe systems usually requires 2 to 3 days to produce gas and has practically no sanitary significance. If *B. coli* cannot produce 10 per cent. of gas in brilliant-green bile in 3 days' time, why worry about it? Even 5 per cent. gas usually means *B. coli,* but some precaution seems necessary against inversion of a small amount of lactose during sterilization. Why hunt for every trace of devitalized *B. coli* and then strive to explain away its presence? Cutting out devitalized *B. coli* yields information of prime importance in reference to typhoid or other water-borne diseases". Even to this day, Dr. Hale is still of the same opinion.[4] Experiments at Mt. Prospect Laboratory, of which he is Director, on the New York Water Supply, demonstrated that gas formation in the test required 1 day when coli cultures were fresh and rejuvenated; 2 days if the sample inoculated was a week old; 3 days if the inoculated water sample was 2 months old. Temperatures of incubation of samples were ice-box, 20° C., and 37° C. Numerous experiments in London, at Mt. Prospect Laboratory, and elsewhere have demonstrated typhoid dies out rapidly in water. In 2 weeks, 90-99 per cent. are dead. In two months practically all are dead. The late Alexander Houston of London has stated that if typhoid organisms survived the storage and treatment of London's water supply, they would be so devitalized that they couldn't cause sickness.

It was not the author's intention to discuss in this article those tests that meet the requirements for the "presumptive test", for such

[3] From a recent private communication.

[4] From a recent private communication.

data were published (7). However, it was observed during this present study that those tests showing 10 per cent. of gas or over during 24 hours' incubation invariably confirmed in B. G. B. and really produced the B. coli Index of Philadelphia's water, which will average about 1/10 the allowable limit set by the U. S. Public Health Service. The remaining group, i. e., 10 per cent. of gas or over between the 24 and 48-hour periods invariably failed to confirm in B. G. B. This group is ordinarily termed *high gas producers* because 75 to 90 per cent. of gas is formed.

Conclusion

Any attempt to attach sanitary significance to those lactose fermenters that do not first meet the preliminary Presumptive Test must be weighed in the light of how often such organisms are encountered during routine examinations of a water supply. Also, what the typhoid fever death rate for the community is, along with other health factors.

For the year of 1941 the typhoid fever death rate for the City of Philadelphia was the lowest in its history, i. e., 0.35 per 100,000. Only 88 cases and seven deaths were reported. Of the 88 cases reported, nearly 20 per cent. contracted the disease while out-of-town or on vacations. Over half of these were infected from eating contaminated raw shellfish. Seven other non-residents were sent to Philadelphia for treatment. Twelve persons contracted the disease from typhoid carriers. Two cases resulted from swimming in polluted water. The source of the other cases was undeterminable. For the first 6 months of 1942 the death rate figure was 0.20.

Each water supply is a problem of its own. In the case of Philadelphia, the frequency of those confirming in B. G. B. is of such a low order of occurrence that they would not appreciatively alter the Coliform Index. As to those that do not confirm in B. G. B., it is of interest to note that they were mainly spore-forming types. Infrequently Gram negative non-spore-formers resembling Coli in size and shape were found that did not ferment B. G. B. These of course were first nurtured along in lactose for 72 hours and then only showed gas between the 48-72-hr. period. When streaked on eosin methylene blue agar they failed to produce growth. What about those tests that did not show gas during 72 hours? Perhaps in 5 or 10 days gas would appear, and they might ultimately be identified as an

aberrant form of B. Coli. The writer's thought as to any of these forms having any sanitary significance, in an otherwise satisfactory water, parallels that of Dr. Hale's (*loc. cit.*) as to "devitalized B. coli".

It seems as if all this could be more adequately expressed by a quotation not original with the author and perhaps not the exact wording "amidst the superfluities of life one must not lose sight of the essentials".

Acknowledgments

The author wishes to acknowledge the splendid spirit of cooperation received from Drs. Hitchens and Hale, the former being the inspirator of the study and the author's counselor, and the latter for lending freely of his personal knowledge and experience. The Staff of the Water Bureau Laboratory showed a splendid *esprit de corps,* and especially to Messrs. Ewer, Rittenhouse and Somers, bacteriologists, must be accredited the actual work.

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CORRECTION

"Modern Antimalarials" by Maximilian Ehrenstein, Vol. 114, Pages 467 and 468: The union between the quinoline ring and the secondary alcohol group at carbon atom 9 is situated at position 4′ of the quinoline residue.

THE RELATION OF pH AND OSMOTIC PRESSURE TO OPHTHALMIC SOLUTIONS

By Louis Arrigoni [1] and Louis Fischer [2]

ALTHOUGH ophthalmic solutions have been used in the treatment of diseases of the eyes since earliest times little attention has been directed toward the therapeutic improvement of this important class of medicaments. The common practice in the preparation of ophthalmic solutions has been and to a large degree still persists in manufacturing them by the simple expedient of dissolving the prescribed therapeutic agents in distilled water or, at best, in normal saline. This almost inevitably results in the preparation of a solution that is irritating to the delicate corneal tissues of the eyes. The degree of irritation may range from a mild sting as in the case of boric acid to an intense burning sensation as experienced with zinc sulfate solutions.

The disadvantages of such an irritant collyrium are twofold. First, the painful burning sensations are very disconcerting to the patient, but more important is the relative therapeutic ineffectiveness of such a preparation. An irritant solution will produce almost instantaneous lacrimation when placed in the eyes and thus wash the medicinal agents from the sphere of their therapeutic action before their beneficial action can be realized.

Recently in the light of new developments in ophthalmology a new trend has been introduced in the preparation of ophthalmic solutions. This trend has been directed toward the elimination of the irritant properties from ophthalmic preparations by making certain adjustments which result in a finished product that more closely simulates the lacrimal fluid. To accomplish this, the osmotic pressure and reaction of pH of the collyria are adjusted to correspond to that of the tear secretions. In most instances, these two adjustments are sufficient to eliminate the irritant properties from ophthalmic solutions.

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Isotonicity and Its Application to Ophthalmic Solutions

Isotonicity may be defined as the tonic relationship that exists when solutions of the same osmotic pressure are found on opposite sides of a semipermeable membrane. This condition of isotonicity, as has already been mentioned, is of great importance in ophthalmic solutions. Unless a solution, which is to be applied to the eyes, is isotonic with the lacrimal fluid sharp and oftentimes painful reactions will result. The irritant properties of a non-isotonic solution can be readily understood by examination of the physical processes that take place in the tissues of the eye during the establishment of osmotic equilibrium between either a hypotonic or hypertonic solution, the lacrimal fluid and the tissue fluids.

If a hypotonic solution is applied to the eyes, the tissue fluids will absorb water from this unadjusted solution and thus cause the delicate corneal tissues to become engorged with fluid. This stretching of the tissue cells results in painful reactions, the severity of which depends on the extent of hypotonicity, i. e., the irritation produced by distilled water is more intense than that produced by a partially adjusted solution. If the collyrium is hypertonic the solution will withdraw water from the tissue fluids until the concentration of solute in the two solutions is essentially equal and osmotic equilibrium has been established between the added solution and the tissue fluids. This withdrawal of water from the tissues causes a dehydration and shriveling of the tissues which also produces painful reflexes.

It can be readily seen from these facts that an isotonic solution is much more efficient and desirable in the treatment of ophthalmic disorders than one whose osmotic pressure must be readjusted by the absorption of water from the tissue fluids as is the case with a hypertonic solution and the loss of water to the tissue fluids as occurs with hypotonic solutions.

Several formulas are available for calculation of the amounts of salts required to make solutions isotonic. One of the simplest and most convenient is the one developed by Nicola (1). This method is based on a constant (0.04307), known as the isotonicity factor of the lacrimal fluid. This constant is formulated from the knowledge that the freezing point of the lacrimal fluid is equal to that of a solution containing 1.4 grams of sodium chloride per 100 cc. of solu-

tion and from the fact that an electrolyte depresses the freezing point of a solution in proportion to its degree of dissociation. Thus a completely dissociated two ion salt in equal concentration will depress the freezing point of water twice as much as a non-electrolyte.

The isotonicity factor is derived from the above facts as follows:

$$\frac{\text{1.4 (per cent W/V of NaCl in lacrimal fluid)}}{\text{58.5 (M. wt. of NaCl)}} \times \text{1.86 (ionization factor of NaCl)}$$

= 0.04307 isotonicity factor of the lacrimal fluid.

The complete formula for the calculation of the amounts of salts required to make an isotonic solution, as presented by Nicola, is as follows:

$$0.04307 \text{ (Isotonicity factor of the lacrimal fluid)} - \frac{\text{per cent of active ingredient W/V in the solution}}{\text{molecular weight of the salt}} \times \text{ionization factor of the salt} \times \frac{\text{molecular weight of salt used to make the solution}}{\text{ionization factor of salt used to make the solution}} = \text{grams of salt per 100 cc. that must be added to make an isotonic solution.}$$

The accuracy of this method for the adjustment of the osmotic pressure of ophthalmic solutions is more than adequate to eliminate any irritant properties that might arise from this source. The only possibility of error, of any consequence, that might result from using this formula may arise from the use of inaccurate ionization factors in certain cases where the ionization characteristics of the salts are indefinite. As a general rule covering the ionization of all salts, Nicola suggests that the following values be used as the ionization factors: 1.5 for salts dissociating into two ions, 2.0 for salts dissociating into three ions, 3.0 for salts dissociating into four ions and 1.0 for weak electrolytes and non-electrolytes such as sugars, gums, etc.

A second comparatively accurate method for the adjustment of the tonicity of solutions takes into consideration the freezing point lowering of the lacrimal fluid, the molal lowering of the freezing point by non-electrolytes (1.86), the molecular weight of the salt used in making the solution isotonic and the ionization factor of the salt (2).

This formula is set up as follows:

$$\frac{\text{Molecular weight of the salt to be used to make the solution isotonic} \times \text{Freezing point lowering by the lacrimal fluid } (-0.80^\circ)}{\text{Ionization factor of salt to be used to make the solution isotonic} \times \text{Freezing point lowering of molal solution of non-electrolyte } (1.86)} = \text{Grams of salt to be added to 1000 prepare a solution isotonic with the lacrimal fluid}$$

gms. of water to

This method is not as convenient as the preceding one in the instances where more than one salt is employed in an isotonic collyrium. In such cases, the freezing point lowering of all the salts, except one, in the particular concentrations used, would have to be available or ascertained when not readily available.

The term ionization factor as used in the preceding paragraphs should not be confused with the more familiar term, ionization constant. The term ionization factor as herein used, refers to the number of moles of both ions and undissociated molecules that result from the dissociation of one mole of a salt in aqueous solution.

For instance, if a two ion salt ionizes to the extent of 80 per cent, then a molal solution of this salt will contain 0.8 moles of positive ions, 0.8 moles of negative ions and 0.2 moles of undissociated molecules, consequently the ionization factor is the sum of these or 1.8.

pH and Its Application to Collyria

In addition to adjusting the tonus of an ophthalmic solution, the reaction or pH of the solution must also be adjusted within

narrow limits of that of the lacrimal fluid if a completely non-irritating and effective collyrium is to be prepared. Lipschutz (3) has shown conclusively that the irritant qualities of solutions applied to the eye are dependent to a large degree upon their hydrogen ion concentration or pH. So marked is the improvement that results from the adjustment of the pH of an ophthalmic solution that some workers attribute the irritant properties of these preparations entirely to the reaction, however, most unbiased observers believe that both the osmotic pressure and the pH must be adjusted to completely eliminate the irritant properties.

The pH of normal lacrimal fluid is commonly accepted to be about 7.4, however, a solution that is within the pH range of 6.5 to 7.8 is relatively non-irritating provided the collyrium is also isotonic with the tears.

Not only must the pH of the solution be made to approximate that of the tears (7.4), but it must also be adjusted so that it will remain at that pH level with only very small deviations. This is accomplished by the addition of buffer salts to the collyrium.

Buffer action is defined as the ability of certain salts, when dissolved in water, to resist a change in pH on the addition of a small amount of acid or base. The term buffer salt is applied both to the salts of weak acids, such as phosphoric and acetic, and to the salts of weak bases.

The principle of buffer action in such cases where a buffer solution is added to a second solution containing a small amount of acid or base can be explained as follows: The addition of an amount of buffer salt relatively large in proportion to the amount of acid or base present causes a fractional decrease of the buffer ion through its union with the hydrogen ion to form the slightly dissociated acid corresponding to the buffer salt employed. This increase in acid has relatively little effect in augmenting the hydrogen ion concentration since by definition it is very weakly dissociated and its ionization is still further repressed by the common ion effect of the buffer salt.

Two precautions must be observed in choosing buffer systems for ophthalmic solutions. First, a buffer system must be chosen that is completely compatible with the active ingredients of the collyrium and second, it must have a relatively high buffering power

over the range in which the preparation is to be buffered. Provided they embrace these properties, any of the common buffer systems are adaptable for use in ophthalmic solutions. A few examples of the more common buffer systems and the pH range in which they have the maximum buffering power are given in the following table:

TABLE I

Buffer Solutions

	pH range
Acetic acid + sodium acetate	3.5— 5.5
Citric acid + disodium phosphate	2.4— 8.0
Boric acid + sodium borate	7.0— 9.1
NaH_2PO_4 + sodium hydroxide	11.0—12.0

The most convenient method for adjusting an ophthalmic solution to a definite pH level is to prepare an acid buffer solution and an alkaline buffer solution, and titrate one against the other until the desired reaction is obtained.

The actual pH measurement of the buffer solutions and the finished product can be accomplished conveniently and accurately by several methods. Two of the more common are the potentiometer and colorimetric methods. The former consists in the measurement with a suitable potentiometer of the potential difference between two electrodes dipping into the solution. This value can be converted to pH by substitution into appropriate equations. The more modern instruments are designed to read directly in pH units thus facilitating its measurement.

The colorimetric method, although more widely used, is far less accurate than the electrometric method. This method revolves around the fact that certain indicators show variations in hue at different pH levels. Making use of this fact, the pH of the solution in question is measured by comparing the color produced when the indicator is added to the solution in question with the color of a series of solutions of known pH containing the same indicator. The pH of the solution is taken to be the same as that of the standard solution which it most closely resembles. Individual variations in color perception make this method less accurate than the potentiometric method.

Other methods such as pH papers are available but are not of sufficient accuracy to be of value in adjusting the pH of buffered ophthalmic solutions.

The application of the principle of buffer solutions to collyria has become increasingly important as the knowledge of the reaction of the lacrimal fluid and its effect in the therapy of the eye in various pathological conditions has increased. For example, it is well established that pneumococcus organisms cannot live at a pH of less than 7.0 and consequently should be treated with an acid collyrium. Streptococcus, on the other hand, requires an alkaline medium for efficient treatment. In general terms, it may be said that conditions causing acidity in the eye should be treated with alkaline collyria and vice versa. Thus, corneal injuries are treated with acid solutions because the injury produces an alkaline condition of about pH 8.4 which must be compensated for efficient treatment. However, it is not sufficient to merely apply a simple alkaline or acid solution, as the case may require, to the eye since the extreme reaction of the lacrimal fluid will neutralize the collyrium and quickly return the reaction to the original level.

To remove this possibility of having an uncontrolled reaction of the lacrimal fluid during the therapy of pathological conditions of the eye, the use of buffered ophthalmic solutions has arisen. The use of buffered solutions of the proper pH for any given pathological condition will immediately bring the pH of the lacrimal fluid to approximately that of the buffer solution and resist any change in pH as long as the buffer remains in the eye.

The authors have undertaken a series of studies on the more common drugs used in ophthalmology. This study is directed toward the formulation of methods for the manufacture of buffered and isotonic solutions of these compounds. The problems involved in the preparation of buffered and isotonic zinc sulfate solutions have been solved and are described in a paper published in the *Archives of Ophthalmology* (4). It is noteworthy of mention that by adjusting the pH of the zinc sulfate solutions to 6.75 with a boric acid-sodium acetate buffer system and making them isotonic with the lacrimal fluid by the addition of alkali chlorides, the irritant properties were completely eliminated. This signal success with the zinc sulfate solutions, which are generally recognized to be very irritating when unadjusted, has prompted the more extensive work that is now in progress.

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THE EDUCATION SERVICE

There is only one service that can increase the mental stature of the individual. There is only one service that can increase the mental and material stature of the Nation—the Education Service.

How much is the nation prepared to spend on this service of education? Let it never be forgotten that such expenditure is real saving—in that it creates wealth. It builds up the effective capital of the nation—capital found in the well being of our citizens and in our material equipment for effective production. To starve education is to cripple all those elements which make for economic and technical advance. Education is not a burden borne on the back of industry. Rather is it true that industry is carried forward on the breast of educational advance.

—President William Griffith, South India Teachers Union.

THE POLICY OF THE NEW JERSEY BOARD OF PHARMACY ON VITAMIN PRODUCTS

When are vitamins foods and not drugs is a question that has bothered many of those responsible for the regulatory laws governing the practice of pharmacy. The Board of Pharmacy of the State of New Jersey has adopted a policy with reference to the sale of such products by other than registered pharmacists. It is reprinted here since it represents an ideal and one which, if it can be maintained after legal tests might well serve as a basis for adoption in other states. —*Ed.*

"A Statement of Policy With Reference to Vitamins and Vitamin Products

Adopted by the Board of Pharmacy of the State of New Jersey
October 5, 1942

Scientific research has shown that vitamins and certain mineral substances are necessary factors in the preservation of health. Normally, both vitamins and minerals are acquired in the daily diet. It is only when the diet is defective and foods are lacking in their normal vitamin and mineral content that it becomes necessary to consider supplementing them artificially.

Certain diseases are caused by vitamin deficiencies. The treatment of such diseases requires vitamin concentrates which will correct the specific deficiency. To determine the deficiencies in the first instance and to diagnose the diseases which result from these deficiencies and to prescribe treatment for them is a medical problem.

Only licensed physicians may diagnose disease and prescribe treatments. When a disease has been diagnosed and the physician has determined that it is due to a vitamin deficiency and he believes that vitamin concentrates constitute the necessary remedy, the vitamins prescribed are drugs.

When vitamin diseases are treated by correcting the diet, either through the use of proper foods or through the proper preparation of foods previously used, or by fortifying or enriching foods artificially with vitamin extracts, the treatment can be considered free from drugs.

The fact that vitamins occur normally in foods but are prepared artificially in the form of concentrates has led to controversy as to whether vitamin preparations should be classified as foods or as drugs.

The problem of nutrition has received considerable attention and study by various scientific laboratories and committees such as the Committees on Food and Nutrition of the National Research Council, the Federal Food and Drug Administration, and others. The Food and Drug Administration after extensive hearings and study has determined the following facts, among others:

(a) Deficiency in the intake of any essential vitamin, mineral, or other dietary property produces pathological conditions known as a deficiency disease, whereas, intake of a certain minimum quantity of such substance prevents the onset of such conditions.

(b) The quantity of a vitamin, mineral, or other dietary property necessary to prevent a deficiency disease is usually less than the quantity necessary for the effective treatment of that disease.

(c) The quantity and the duration of administration of such a property for the correction of such disease may differ under different conditions.

(d) Purchasers in general are unaware of the quantities of dietary constituents or the duration of their consumption necessary for the effective treatment of deficiency diseases.

(e) The terms 'vitamin B_1' and 'thiamine', the terms 'vitamin C' and 'ascorbic acid', and the terms 'riboflavin', 'vitamin B_2' and 'vitamin G', are synonymous.

(f) Deficiency in the intake of vitamin A produces the pathological conditions known as nutritional night blindness and as xerophthalmia.

(g) Deficiency in the intake of vitamin B_1 produces the pathological condition known as beriberi.

(h) Deficiency in the intake of vitamin C produces the pathological condition known as scurvy.

(i) Deficiency in the intake of vitamin D produces the pathological conditions known as rickets and osteoporosis.

(j) Deficiency in the intake of riboflavin produces the pathological condition known ae ariboflavinosis.

(k) The minimum daily requirements for such vitamins and minerals in the human diet are the quantities necessary for the prevention of such deficiency diseases.

(l) The requirements of different persons for most of the essential vitamins bear a relationship to body weight which in turn bears a relationship to age groups. Thus, for nutritional purposes, with respect to these and many other dietary factors, persons are commonly classed as infants (persons under one year of age), children (persons one or more but less than 12 years of age), and adults (persons 12 or more years of age); children may be further classified as the groups less than six, and six or more years of age, when nutritional requirements bear an unusually close relationship to body weight.

(m) Purchasers generally do not know the quantity of vitamins and minerals needed to supply their minimum daily requirements.

(n) Because of variations in body weight and other factors, the minimum daily requirements of individuals for vitamins vary, even among persons in the same age groups; but in the cases of vitamins A, B_1, C, D, and riboflavin the variation within any age group is of such narrow range that a minimum daily requirement for any such vitamin can be prescribed for different age groups, and the ingestion of the quantity so prescribed will prevent any clinically significant manifestation of the deficiency disease characteristic of deficiency of such vitamin.

(o) The minimum daily requirement for vitamin A is as follows:

For infants, 1500 U. S. P. units.

For children more than 1 but less than 12 years of age, 3000 U. S. P. units.

For any person 12 or more years of age, 4000 U. S. P. units.

(p) The minimum daily requirement for vitamin B_1 is as follows:

For infants, 0.25 mg. (83 U. S. P. units).

For children more than 1 but less than 6 years, 0.5 mg. (167 U. S. P units).

For children 6 or more but less than 12 years old, 0.75 mg. (250 U. S. P. units).

For a person 12 or more years old, 1 mg. (333 U. S. P. units).

(q) The minimum daily requirement for vitamin C is as follows:

For infants, 10 mg. (200 U. S. P. units).

For children more than 1 but less than 12 years old, 20 mg. (400 U. S. P. units).

For a person 12 or more years old, 30 mg. (600 U. S. P. units).

(r) The minimum daily requirement for vitamin D is 400 units for any person, irrespective of age, except in respect of vitamin D contained in cows' milk and evaporated milk under certain conditions.

(s) The minimum daily requirement for riboflavin is as follows:

For an infant, 0.5 mg.

For a person 12 or more years old, 2.0 mg.

The minimum daily requirement for riboflavin for children one year or more but less than 12 years of age has not been established.

It is apparent from the foregoing that in order for an individual to determine whether or not he should consume any vitamin product, he must determine first of all whether the normal daily intake of vitamins from the foods which are eaten is sufficient, and secondly, whether he should add to his daily vitamin intake without medical advice. In order to determine this, one must know what the normal vitamin intake should be for the specific individual and what vitamins are commonly found in the food consumed. Only with such knowledge is a layman in a position to supplement his diet intelligently with vitamin products offered for sale.

If a vitamin product is marketed only for the purpose of supplementing the diet and the label supplies adequate information as to normal intake of each vitamin contained in the preparation and the amount of each such vitamin contained in the product, and if it is not held out for the treatment of any disease but merely as a food accessory, the Board of Pharmacy of the State of New Jersey will not classify such product as a drug, provided the label of such product bears the additional statement: "Not for Medicinal Use."

On the other hand, any vitamin preparation which is held out to be a treatment for any deficiency disease or for the correction of any symptoms of disease or for the prevention, mitigation or cure of disease, either by direct statement or by inference, must be considered a drug or medicine within the meaning of the Pharmacy Act and, as such, it may be sold only under the supervision of a Registered Pharmacist.

The public is urged to remember that vitamins in concentrated form are unnecessary to the individual receiving a properly balanced diet and that proper food is the best source of necessary vitamins. It is up to a physician to decide if and when vitamins are needed for the treatment or prevention of disease, and in such cases the concentrated vitamins in the usual capsule form in proper dosage may be prescribed, and, of course, in such cases they are drugs.

So that there may be no misunderstanding in the public mind as to the type of vitamin preparation which is being offered for sale, concentrated vitamin preparations which are sold exclusively as foods or food accesories and the labels of which bear no directions for use in the prevention, mitigation or cure of disease must be labeled *"Not for Medicinal Use."* Otherwise they will be considered as coming

within the classification of drugs and medicines within the meaning of the Pharmacy Act.

If the product is sold as a drug or medicine for the prevention, mitigation or cure of disease, it is, of course, a drug and must bear adequate directions for use as a drug, and under the provisions of the New Jersey Pharmacy Act such products can be sold only by or under the supervision of a Registered Pharmacist.

Nothing in this statement of policy is to be construed as relieving any producer or distributor of vitamin products in interstate commerce from full compliance with all requirements for labeling under the Federal Food, Drug and Cosmetic Act and Regulations.

THE BOARD OF PHARMACY OF THE
STATE OF NEW JERSEY.

ROBERT P. FISCHELIS,
Secretary."

SELECTED ABSTRACTS

Interesting Summaries of Recent Papers

Dangerous Effects of Vitamin D Overdosage on Dental and Paradental Structures. By H. Becks. *J. A. D. A. 29,* 1947 (1942). In order to study more completely the effects of vitamin D overdosage on both tooth and bone structure the authors studied the effects of various levels of vitamin A and D dosage in a group of dogs. A summary of their findings is as follows:

1.—Optimum amounts of vitamins A and D in the form of halibut and tuna liver oil helped produce strong jaw bones and teeth.

2.—Optimum amounts of vitamin D with excessive amounts of vitamin A seem to be still more favorable for growth and development of jaw bone and dental structure.

3.—Excessive amounts of vitamin D in the form of irradiated ergosterol with optimum amounts of vitamin A led to a generalized osteosclerosis of the bone and paradental bone structures. Teeth were malformed and in malocclusion.

4.—Excessive amounts of vitamins D and A derived from tuna liver oil seemed to be less dangerous from the standpoint of pathology than when the vitamin D is derived from irradiated ergosterol.

5.—Excessive amounts of vitamins A and D in the form of halibut liver oil and irradiated ergosterol, respectively, also produced osteosclerosis but far less pronounced than when only optimum amounts of A were given.

From these results it would appear that the natural fish oils are far less dangerous than irradiated products and further that excessive amounts of vitamin A decreases the injurious effects of excess of vitamin D. It is also evident that excessive overdosage of vitamin D is not without great potential danger.

Sterilization of the Sulfonamides. W. J. Buckland, *Pharm. J., 95,* 112 (1942). Sulfonamides may not be sterilized with the dry heat method. Autoclaving usually leads to caking, particularly with sulfanilamide, which is quite soluble in water. Several different meth-

ods of autoclaving sulfanilamide were tried but in each case crystallization with subsequent caking occurred. Autoclaving followed by vacuum drying still did not prevent crystallization and caking. The theory was evolved that the cause of this difficulty might be steam condensing on the cold surface of the powder and the cold inner surface of the containers used. This proved to be the case and the probable cause of all trouble.

When tubes containing sulfanilamide were allowed to preheat in the autoclave before turning on the steam no difficulty was experienced.

The method used was as follows:

(1) The apparatus consists of an autoclave with vacuum-drying fixture (a hospital dressing sterilizer). Dry boiling tubes are used as containers and plugged with non-absorbent cotton.

(2) The jacket pressure of the sterilizer should be ready at a pressure of 20-30 lb.

(3) Allow the steam to enter the chamber of the autoclave until 20 lb. pressure is indicated and leave for 5 minutes.

(4) Using the appropriate valves clear the chamber of all steam and water formed by condensation. This process has heated the chamber, and the boiling tubes with loosely made plugs of non-absorbent cotton are now placed inside. They should be on their sides with the powder spread over their full length, giving a thin mass for the steam to penetrate.

(5) Leave for 15 minutes in the hot autoclave, then autoclave for one-half hour at 15 lb. pressure. During this process the water escape valve should be slightly open to allow any water which might form by condensation to escape as soon as possible.

(6) Clear the chamber of steam quickly and start the vacuum immediately. If any time for cooling is allowed between autoclaving and drying, condensation of steam in the powder will occur with resultant caking.

(7) Remove the tubes from the autoclave, place a tight sterile plug on top of the one already in place and cap the tubes by any suitable method.

Caking does not occur. If apparent caking is observed, it is present only in the hot powder and when cool a tap on the side of

the tube is all that is necessary to show that the sterile preparation is in the form of soft powder.

The efficiency of sterilization was proven using both *S. aureus* and *B. Welchii.* Sulfathiazole and Sulphapyridine are even more easily handled than Sulfanilamide by this method. A very plausible theory is evolved by the author explaining the mechanics of both caking and its prevention.

The Rate of Absorption of Sulfonamides In Vitro and In Vivo After Local Application. A. T. Fuller, F. Hawking and M. W. Partridge, *Quart. J. Pharm. & Pharmacol. 15,* 127 (1942). The authors have devised a mechanical means of estimating the rate of absorption of sulfonamides *in vitro* and these results are correlated with *in vivo* experiments. In the latter the sulfonamide was applied to a standardized wound in rabbits and the rate of absorption was estimated by measuring the excretion in the urine. A satisfactory agreement between the two technics was obtained. On the basis of the results obtained the following discussion is presented. When inserted into a wound, sulfanilamide will be rapidly dissolved producing a high initial concentration in the fluids of the wound but one which will not last more than one or two days, Sulfapyridine and sulfadiazine will be dissolved more slowly producing a lower initial concentration but one which would be sustained longer. Sulfathiazole occupies an intermediate position. The different behavior of the four compounds is presumably due to their differences in solubility. Since the therapeutic value of these compounds depends on bacteriostatic action rather than on a bactericidal one, it is probable that the duration in a wound is more important than the initial concentration. On the other hand, low solubility may hinder the attainment of an effective bacteriostatic concentration unless compensated by higher activity and too slow absorption leads to the formation of solid cakes which act like a foreign body. A mixture of sulfanilamide and one of the less soluble ones, e. g. sulfathiazole might be advantageous.

SOLID EXTRACTS

Paragraphs of Scientific Interest Presented in Review

Man has finally achieved a long sought for technique, namely, sex control. This has now been accomplished using a certain species of fly known as Drisophila melanogaster and either 100 per cent. males or 100 per cent. females may be produced at will. This is a long way from sex determination with humans but considerable data on this problem has been accumulated.

AJP

In many countries a wife who fails to produce a son is in disgrace. It is now known that human sex is determined by the presence or absence of a particular gene or set of genes of the father rather than by the mother. No longer may the wife be blamed for failure to produce the wished-for son!

AJP

Oleomargarine once thought to be a poor substitute for butter has been shown to be just as nutritious. Originally it was lacking in vitamin A but this is now added in amounts equal to that present in butter. Demand for "Oleo" now exceeds the supply due to the butter shortage and the shortage of oils used in its manufacture.

AJP

When will we adopt a really effective program for the eradication of syphilis? Blood examinations of about a million selectees indicate that almost 1 in 20 of all young men have syphilis and, with the Negro group alone, the incidence is about 1 in 4. In a civilized country such figures point out what is almost a national disgrace! Syphilis control is well understood. Why not treat this condition the same as any other and not continue to put it in some special class for so-called "moral reasons."

The field of photography, noted for its perfection and marvelous advancement since its inception, is not so old as its progress would indicate. This is brought to mind very forcefully by the recent observance of the hundredth anniversary of the founding of the first photographic business establishment by Edward Anthony, a pupil of Samuel F. B. Morse, inventor of the telegraph. When one considers the marvels of color photography and all of the other ramifications of the art, a hundred years does not seem enough time for such great developments.

AJP

It has often been said that the development of the airplane has, in some respects, reached its zenith because the human body could not stand greater speeds or heights. This thesis is accentuated by the recent attainment by two Army pilots of a speed of 725 miles per hour—12 miles a minute—in a diving Republic P-27 Thunderbolt. Starting at a height of 35,000 feet and leveling off at 25,000 feet, they traveled faster than sound at that altitude. But the pressure was so great that it was almost impossible for the pilots to move their arms and legs to control the plane.

AJP

Substitution is a term that is not altogether acceptable to pharmacists, but the War Engineering Board has capitalized upon the ability to utilize substitute substances where no harm results and where economies are effected. For instance, in the production of M-4 tanks, substituted materials, equally as good as the original parts, allowed for an estimated annual saving of 7,000,000 pounds of nickel, 2,000,000 pounds of chromium, and nearly 1,000,000 pounds of molybdenum. In another operation on truck headlight reflectors, 65,000 pounds of copper, 32,000 pounds of zinc, 275 pounds of nickel and 160 pounds of silver are being saved for every 100,000 vehicles so outfitted.

AJP

BOOK REVIEWS

Malaria and the Antimalarials (With special reference to Southeastern Asia). By *Dr. Aubrey H. Hamilton, Lieutenant-Commander, MC-V(S), U. S. N. R.* Prepared with the collaboration of and under the auspices of the *Board of Economic Warfare* (Far Western Division, Netherlands Indies Section and later the United Nations Division) and of the *Department of Commerce* (Division of Drugs and Chemicals). About 140 mimeographed pages and 2 maps.

This is an up-to-date review written primarily for persons who are concerned with the prophylaxis and treatment of malaria. The report is based partly on the author's twenty years experience in Java and Southeastern Asia, and partly on the literature. In particular the antimalarial drugs are discussed from the viewpoint of their toxicity, mode of administration and dosage. It is pointed out that the formerly administered doses of quinine are too high. Lower doses will serve the same therapeutic purpose, cause fewer toxic symptoms and will, in addition, tend to conserve the present stocks of cinchona alkaloids. In the author's opinion the total amount used per case can be reduced to about one-third or less of the former requirements (for prophylaxis as well as treatment).

The consensus of clinical opinion in the orient is that the hydrochloride of quinine is superior to the sulfate. The greater effectiveness is due to something more than the larger amount of quinine base present in the hydrochloride. It seems as if the introduction of the halogen ion into the salt tends to enhance its effectiveness out of proportion to the mere ratio of base present.

Totaquine, as defined in U. S. P. XII, is subjected to a thorough discussion from the viewpoint of its manufacture as well as its therapeutic use. In the author's opinion totaquine is approximately half as efficient, weight for weight, as quinine. This assumption is based on his clinical experience with the various cinchona alkaloids, whose relative potencies are estimated as follows:

Quinine hydrochloride	100 (standard)
Quinidine hydrochloride	100

Quinine sulfate	80
Quinidine sulfate	75
Cinchonine salts	50
Cinchonidine salts	25
Quinoidin	5

The author discusses the adjuvant action of epinephrine in treating malaria. When this substance is used, it should be administered hypodermically about 10 minutes before quinine is given. "It seems probable that the use of adrenalin causes a contraction of the vessels of the splanchnic area, or perhaps, splenic contraction and so tends to drive out of their possible nestling place in the spleen and elsewhere such parasites as might otherwise find refuge there from the action of the substances called to activity by the quinine."

The author opposes the synthetic antimalarials, plasmochin as well as atabrine. Although the limitations regarding the use of plasmochin are generally recognized, his rather gloomy outlook regarding atabrine is not shared by a number of other reviewers of this subject. The author states, "Of course, circumstances may arise compelling the use of atabrine in view of the shortage of quinine and cinchona products, but this would appear to be a situation deeply to be regretted". According to the author's opinion atabrine should not be used for prophylactic purposes. In the treatment of malaria it should only be applied to first cases. All relapses should be treated with quinine.

Whether the dangers due to the toxic properties of atabrine are as great as the author sees them, must be left to the judgment of experts in the field. At any rate, the manufacture of atabrine in this country has reached the high level of about one billion tablets per year, and the Subcommittee on Tropical Diseases of the National Research Council recommends its use for prophylactic as well as therapeutic purposes (See Journ. Amer. Med. Assoc. *120,* No. 13 (Nov. 28, 1942), page 1043). Large orders for atabrine have been placed by the U. S. Government.

In a brief chapter the author discusses the Malaria Problem in the United States. He tries to obtain a fair estimate of the annual number of malaria cases. For this purpose he selects three avenues of approach and arrives in each case at a figure of about two million.

In conclusion it may be said that Dr. Hamilton's review on Malaria and the Antimalarials is a comprehensive presentation of

the subject matter. Various detailed schedules of dosages of antimalarials are given. The study of the review is recommended to anyone who is concerned with the prophylaxis and treatment of malaria.

MAXIMILIAN EHRENSTEIN.

Textbook of Pharmacognosy. By Heber W. Youngken, A. M., Ph. M., Ph. D., Sc. D. Professor of Pharmacognosy and Biology in the Massachusetts College of Pharmacy, Boston. Fifth edition. The Blakiston Company, Philadelphia, Pa., 1943. XIV + 1038 pages, 511 illustrations. Price: $7.50.

The fifth edition of this well-known American textbook of Pharmacognosy conforms to the standards of the U. S. P. XII and the N. F. VII, and therefore throughout the work, the necessary changes, deletions and additions, have been made in the monographs of the official drugs. At the same time, the author has placed in one volume a veritable mine of information concerning many non-official drugs.

Compared with the previous edition, the text has been increased by over 100 pages, and there are many additional illustrations. Some of the older and less-suitable figures have been replaced.

The general plan of the work remains the same, namely—after an introductory morphologic consideration of drugs (Part I pp. 3-51), the greater part of the volume is taken up by a study of drugs arranged according to their taxonomic classification (Part II pp. 61-969). Between the two parts, a chapter has been added dealing with therapeutic classification. The consideration of drugs of animal origin follows that of drugs of plant origin. The chapter on microanalytical methods has been retained. (pp. 970-984.)

The new volume is not merely a repetition of the older fourth edition revised by the introduction of the above-mentioned changes, but the user will soon discover that the text has been modernized, monograph by monograph with the result that each article will repay most careful reading.

Among the new monographs, dealing with drugs of vegetable origin, may be mentioned the following: Perpolitiones Oryzae, Potentilla Anserina, Schinopsis, Anhalonium, Strychnina, Totaquina and Quinina.

Certain other monographs, although not new, have been materially enlarged. For example, the discussion of Ergota has been augmented by a consideration of allied Ergots; the Caryophyllus monograph has an added histology section; Ecuadorian Sarsaparilla has been added to the table of "Distinctions between Official Sarsaparillas"; the Digitalis monograph includes an outline of the cat assay method.

In various monographs (Majorana, Lavandula, Salvia, etc.) stress has been placed upon the cultivation of the plant yielding the drug, thus reflecting the increased emphasis upon this phase of pharmacognosy occasioned by the present war.

To the chapter dealing with drugs of animal origin, the following articles, among others, have been added: Creta Præparata, Hirudo, Os Sepia, Crotalus Antitoxin, and Bothrops Antitoxin. In the endocrine gland products section, there are articles dealing with Testosterone and Estrogenic Hormones.

Among the new illustrations may be listed those dealing with the structure of Pinus Alba, Oryza sativa, Granatum, Coca, Buchu, Aletris, Scilla, Dioscorea, Hydrastis, Sassafras, Cinnamomum Zeylanicum, Apocynum, Capsicum, Viburnum, Coccus and Cantharides.

The subject matter throughout the work is treated clearly and logically—a way which is particularly pleasing to the busy student, teacher and research worker. The author makes effective use of tables and illustrations.

It is a pleasure to welcome this up-to-date, well-balanced and stimulating contribution to the science of modern pharmacognosy. It is a "must" volume for all whose path in any way touches this field.

M. S. DUNN.

Accounting and Record System for the Retail Pharmacy. Published and Distributed by Eli Lilly and Company, Indianapolis, Ind.

This is a well planned bookkeeping and record system specifically adopted to the use and needs of the retail pharmacist of today. Requiring but a minimum of time to be kept up to date, it will provide the necessary information regarding the financial condition of

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HARVEY P. FRANK.

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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